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Confronting SARS: a view from Hong Kong

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Severe acute respiratory syndrome (SARS) emerged as a new disease in Guangdong Province, People's Republic of China in late 2002. Within weeks it had spread to Hong Kong and thence globally to affect over 25 countries across five continents. The disease had the propensity to cause clusters of pneumonia, particularly in healthcare workers or close family contacts. A global effort coordinated by the World Health Organization successfully defined the aetiology, epidemiology and clinical characteristics of the disease, and the implementation of case identification, isolation and infection control measures led to the interruption of the global outbreak by July 2003. The pattern of disease emergence and strategies for control of SARS provides lessons for coping with future emerging infectious disease threats.

Keywords: SARS; emerging infections; pneumonia; influenza; laboratory diagnosis

1. EMERGENCE OF A NEW DISEASE

News of an outbreak of 'atypical pneumonia' circulating in Guangdong Province reached Hong Kong in early February 2003. Residents in Guangzhou, the provincial capital of Guangdong, were reportedly rushing to buy masks, antibiotics and traditional remedies including white vinegar, the boiling of which was believed to ward off respiratory infections (Rosling & Rosling 2003). At this time, the health authorities of the Hong Kong SAR and Guangdong did not have efficient channels for exchanging information on matters of health on a 'real-time' basis (SARS Expert Committee 2003). By 11 February, the People's Republic of China had informed the WHO of an outbreak of an acute respiratory syndrome with 305 cases and five deaths in Guangdong Province (WHO 2003*a*). The disease had been circulating in Guangdong since November 2002. It was a severe viral pneumonia that failed to respond to antibiotics including β-lactams and macrolides. The most notable characteristic was the propensity to cause clusters of disease in family contacts and healthcare workers, and in recognition of this the disease had been named 'infectious atypical pneumonia' (Zhong & Zeng 2003). Some of the patients with this disease in Guangdong during November and December 2002 had a history of occupational or other exposure to markets or restaurants involved in the live game animal trade (Breiman *et al.* 2003; Zhong *et al.* 2003). Several aetiological agents were under consideration including *Chlamydia*.

2. SURVEILLANCE AND AETIOLOGY

In response to this information, on 14 February the Hospital Authority and Department of Health in Hong Kong set up surveillance for cases of severe atypical pneumonia admitted to public hospitals. The Hospital Authority of Hong Kong manages all public hospitals accounting for more than 90% of all hospital admission within Hong Kong SAR. However, community-acquired pneumonia is a common disease in all parts of the world and Hong Kong SAR (population 6.8 million) had *ca.* 1400 episodes of disease every month, with 55–75 of them requiring management in intensive care units (SARS Expert Committee 2003). It was clear from the outset that an indicator with such a high baseline would not provide early warning of a new disease. Therefore, surveillance focused on severe community-acquired pneumonia and included intensive microbiological investigation of all such cases. Those patients with recent travel to Guangdong received particular attention, though microbiological investigation was not restricted to this group.

By mid-February, aetiological diagnoses in patients with atypical pneumonia in Hong Kong included *Chlamydia psittaci*, *C. pneumoniae*, adenovirus, parainfluenza, rickettsia, influenza A, influenza B, mycoplasma and pyogenic bacterial infections. However, there was nothing remarkable in these findings that would explain the unusual outbreak of disease in adjoining Guangdong. Furthermore, there was no significant difference in pattern of aetiological agents in patients with or without a history of recent travel to mainland China. The first finding of note came on 20 February with influenza A subtype H5N1 being isolated from two members of the same family who had returned to Hong Kong from a visit to Fujian (WHO 2003*b*; Peiris *et al.* 2004). After the 'bird flu' outbreak in 1997, this was the first time that H5N1 viruses had been isolated from humans. In the context of the ongoing pneumonic disease of unknown aetiology in Guangdong, the WHO and its influenza network activated emergency pandemic response plans.

However, intensive investigation of other patients in Hong Kong, as well as some clinical specimens from patients in Guangzhou investigated in collaboration with

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Professor Nanshan Zhong (Zhong *et al.* 2003) revealed no further cases of influenza A (H5N1) infection. Some patients had evidence of influenza A (H3N2) infection. The possibility of a reassortant human H3N2 virus that had acquired the internal genes of an avian virus or the emergence of a drift mutant was considered. Genetic analysis of these isolates from Guangdong did not reveal such reassortment.

On 26 February, there were reports of an outbreak of respiratory disease in healthcare workers in a hospital in Hanoi. Carlo Urbani, the WHO epidemiologist who alerted WHO to that cluster of cases, sadly succumbed to the disease himself. By 11 March, a large cluster of cases was being reported from the Prince of Wales Hospital in Hong Kong (Lee *et al.* 2003). Within Hong Kong, our own efforts focused on patients with pneumonia outside of that large cluster of cases at Prince of Wales Hospital. In response to these outbreaks, WHO issued a global alert on 12 March (WHO 2003*c*). By 14 March, further clusters of patients were reported in Singapore and Toronto. By 15 March, WHO had received over 150 reports of this new disease from outside of mainland China. The disease was named SARS, a preliminary case definition was provided and WHO issued a travel advisory warning against travel to affected regions.

On 17 March, WHO initiated a network of laboratories across the world to help to establish the aetiology of this new disease. The network functioned through daily teleconferences exchanging information on patients and specimens being investigated on a real-time basis. In addition, a secure Web site was established to post findings that could be shared by members within the network (WHO Multicentre Collaborative Network for SARS Diagnosis 2003). The overall clinical picture and the lack of a response to antibiotics suggested a viral cause. The clinical features of the disease have been described in detail elsewhere and will not be reviewed here (Lee *et al.* 2003; Peiris *et al.* 2003*c*; Tsang *et al.* 2003; Jernigan *et al.* 2004). Conventional microbiological investigations failed to reveal an aetiological explanation for the illness in the patients with suspected SARS. Similar findings were being echoed by members of the WHO network laboratories who were investigating patients from Vietnam, Singapore, Toronto and Germany. As a result, we turned our search to look for novel viral pathogens.

By 18 March, laboratories within the WHO laboratory network reported sighting paramyxovirus-like particles by direct electron microscopy on respiratory specimens from patients with SARS. In addition, detection of human metapneumovirus RNA in clinical specimens by RT–PCR was reported from laboratories in Hong Kong and Toronto. Between 21 and 24 March, three laboratories within the WHO network of laboratories, including our own, independently reported the isolation of a novel coronavirus associated with SARS (Drosten *et al.* 2003; Ksiazek *et al.* 2003; Peiris *et al.* 2003*a*).

In our own laboratory, the strategy in searching for a novel virus associated with SARS included the use of consensus primer or low stringency based RT–PCR to search for viruses related to, though not identical to, known viral pathogen groups, random RT–PCR methods, the use of cell lines not usually used for diagnosing conventional respiratory viruses and electron microscopy on tissue specimens, when available. One of the cell lines included in our panel of cells was FRhK-4: a cell used to grow hepatitis A virus. Over the past year, we had found FRhK-4 cells able to support the replication of several respiratory viruses including human metapneumovirus, a virus with fastidious growth requirements (Peiris *et al.* 2003*b*). A lung biopsy from one patient and a nasopharyngeal aspirate from another showed evidence of a subtle cytopathic effect on FRhK-4 cells which became more pronounced on passage (figure 1*a*). Using infected cells as antigen in an indirect immunofluorescence assay (figure 1*b*), we were able to demonstrate seroconversion or rising antibody titres in sera of several patients with suspected SARS. Paired sera from patients with atypical pneumonia as a result of other causes were seronegative. Thus, there was a close link between the novel virus and SARS. Thin section electron microscopy on infected cells clearly showed evidence of abundant virus particles in the Golgi–endoplasmic reticulum complex and on the surface of infected cells. Electron microscopy of infected cell supernatants using negative staining showed evidence of virus particles of 60–80 nm with a morphology compatible with coronaviruses. Electron microscopic examination of the lung biopsy that yielded the virus isolate revealed viral particles similar in morphology to that seen in virus-infected cells *in vitro*.

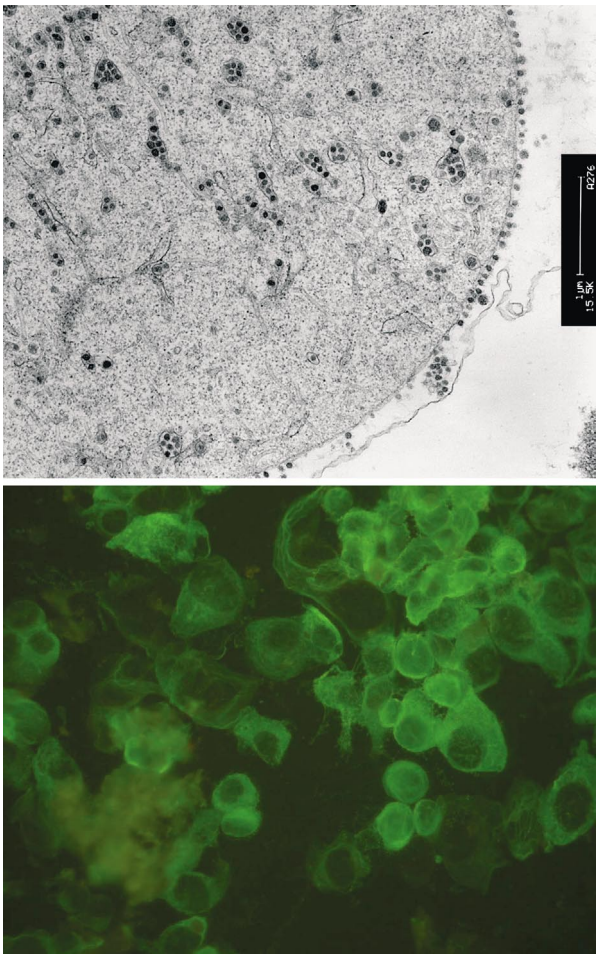

Figure 1. (*a*) Thin section electron micrograph of FRhK-4 cells infected with SARS coronavirus (courtesy of J. M. Nicholls). (*b*) Convalescent serum from a patient with SARS reacting in an indirect immunofluorescence test with SARS coronavirus infected FRhK-4 cells.

Genetic sequencing of gene products amplified by random RT–PCR differentially expressed on infected and uninfected cells yielded a 624 bp fragment of genetic sequence with homology to the replicase gene of the Coronaviridae. However, the extent of genetic homology to known coronaviruses was not high and we suspected that we were dealing with a novel coronavirus (Peiris *et al.* 2003*a*). We established evidence of SARS-CoV infection by serology or RT–PCR in 45 out of 50 patients with SARS whereas there was little evidence of virus activity in community controls (Peiris *et al.* 2003*a*). These findings provided evidence of the association between this novel coronavirus and SARS. Using Vero-E6 cells, similar findings were being reported to the WHO laboratory network from the Centers for Disease Control, Atlanta and the Bernhard Nocht Institute for Tropical Medicine, Hamburg, who were investigating patients originating from Vietnam and Singapore, respectively (Drosten *et al.* 2003; Ksiazek *et al.* 2003). Independent reports of a novel coronavirus from three laboratories investigating patients from three countries provided a compelling case for the link between the novel virus (now named SARS-CoV) and SARS. Confirmation of Koch's postulates was achieved by reproducing the disease in cynomolgous macaques after experimental inoculation with SARS-CoV (Fouchier *et al.* 2003; Kuiken *et al.* 2003; reviewed by Osterhaus *et al.* 2004). The full genetic sequence of the SARS-CoV was unravelled within weeks of its initial isolation, providing the biological foundation for further research on antivirals, vaccines and pathogenesis (Marra *et al.* 2003; Rota *et al.* 2003).

3. LABORATORY DIAGNOSIS

The identification of the SARS-CoV as the presumptive aetiological agent of SARS immediately provided two options for laboratory diagnosis: a serological test, initially based on indirect immunofluorescence on virus-infected cells and an RT–PCR test based on the partial genetic sequence then available. Initial indirect immunofluorescent tests with blood donor sera on SARS-CoV infected cells gave negative results suggesting that SARS-CoV was not previously endemic in the human population (Ksiazek *et al.* 2003; Peiris *et al.* 2003*a*). It also indicated that the immunofluorescent test could be a useful serological test for diagnosis of SARS. On 28 March, just a week after the aetiological agent was identified, we began laboratory testing for SARS based on these two tests with the caveat that these were experimental tests still under evaluation. Under normal circumstances, one would not provide a diagnostic service without careful prior evaluation and validation. However, these times were far from 'normal': the need for the diagnostic service was here and now, not sometime in the future, when the test may be better validated but the need may have passed. However, providing such a diagnostic service was fraught with problems. We were swamped with diagnostic test requests from across Hong Kong, with over 200 specimens arriving per day at our laboratory alone. There were initially two and then three laboratories providing serology and RT–PCR diagnosis. Clinical data on many of these patients were difficult to obtain and therefore evaluation of the performance characteristics of the tests on a real-time basis proved difficult. In general, data-capture and data-flow proved to be a major obstacle in reacting to the SARS crisis. The sudden and large workload hampered further optimization and test development in the short term. In subsequent months, the Hospital Authority of Hong Kong consolidated all the clinical and laboratory data into one database (designated e-SARS) thereby facilitating much better data analysis. Such a system would be invaluable in dealing with emerging infectious disease outbreaks in future.

It became clear that whereas serology was reliable at providing retrospective diagnosis of SARS within the context of this outbreak, diagnosis early in the illness was difficult to achieve. Seroconversion occurred only around day 10 of disease or later. Surprisingly, RT–PCR for SARS-CoV yielded more positive results later in the course of the illness when compared with the first 5 days of illness (Chan *et al.* 2004; Poon *et al.* 2003*a*,*b*). This contrasts with other respiratory viral infections where viral detection rates decrease in later stages of disease. Thus, these first generation SARS-CoV tests had limited value in screening patients suspected to have SARS for purposes of triage.

4. EPIDEMIOLOGY AND CONTROL

Within weeks of SARS appearing in Hong Kong, a travel and business hub for the region, the disease had spread to affect over 8000 patients in 26 countries across five continents. Hospitals served as amplifiers of the disease and SARS exposed the logistical problems of coping with an epidemic of infectious disease in the twenty-first century and highlighted the weak links in infection control within hospitals, especially in tertiary hospitals providing modern invasive care. Determined and concerted global public health measures by case detection using a clinical case definition and patient isolation, succeeded in interrupting the chain of disease transmission and by 5 July 2003, the outbreak was formally declared as over. The understanding of the aetiology and the availability of diagnostic tests no doubt contributed to this success. But it is not clear whether the public health interventions may have achieved the desired result irrespective of such knowledge of aetiology. However, a better understanding of the causative virus did prove invaluable in several respects that were pertinent for control of SARS. Virus was isolated from the faeces and urine as well as the respiratory tract, suggesting that the infection was not confined to the respiratory tract. Furthermore, because SARS-CoV was unusually stable in the environment, including in faeces (WHO 2003*d*), the possibility of faecal transmission had to be considered. These findings provided the basis for understanding the community outbreak at Amoy Gardens, where over 300 patients were infected within a few days and where contaminated sewage may have played a role in transmission of infection (Yu *et al.* 2004). Quantitative RT–PCR assays on longitudinally collected specimens from the same patient showed that SARS-CoV viral load in the upper respiratory tract was low in the first 5 days of illness and increased progressively to peak at around day 10 after disease onset (Peiris *et al.* 2003*c*). This was in contrast with most other respiratory viral infections where maximal viral load in the respiratory tract occurs soon after the onset of clinical disease. These findings explained the epidemiological observations that transmission was more common after the first 5 days of illness (Lipsitch *et al.* 2003). The

unusual stability of SARS-CoV may also explain the propensity of this virus to spread so readily in a hospital setting. The low viral load in respiratory secretions early in the disease suggested that diagnostic tests applied to upper respiratory tract specimens would have to be pushed to the limits of sensitivity to diagnose disease in the first few days when viral loads are very low. Later modifications of RT–PCR test strategies based on real-time RT–PCR together with enhanced RNA extraction methods allowed higher success rates in diagnosis of patients in the first few days of illness (Poon *et al.* 2003*b*).

5. ANIMAL ORIGINS

The fact that there was little serological evidence of SARS-CoV in the general population indicated that this was a virus of animal origin that transmitted to humans relatively recently. The anecdotal reports of the early patients with SARS having contact with the live wild animal restaurant trade suggested that live wild game markets that were prevalent in Guangdong and other parts of mainland China may be the initial source of the virus infecting humans. Investigation of these wild game markets revealed the presence of a closely related virus in several small mammalian species, most notably the palm civet cat (*Paguma larvata*). Persons working directly in this trade had high prevalence of antibody to the SARS-CoV and related animal viruses (Guan *et al.* 2003). The recent re-emergence of SARS in humans was also linked to the animal trade (see the accompanying article by Zhong 2004).

6. WHAT NEXT? LESSONS FROM SARS

It is interesting that the techniques that played the key roles in identification of the aetiological agent of SARS in all three laboratories were the traditional methods of cell culture and electron microscopy (Drosten *et al.* 2003; Ksiazek *et al.* 2003; Peiris *et al.* 2003*a*). Similar strategies were instrumental in the discovery of other recent novel pathogens including Nipah virus and human metapneumovirus. In this age of high-throughput genomics, it is important that expertise in methods of 'classical virology' are not neglected and lost. Given budgetary constraints imposed by 'managed care' and repeated 'efficiency gains' in the health systems of many countries, there is the perceived need for diagnostic virology laboratories to be primarily accountable for patient care (i.e. providing rapid diagnosis) rather than for public health. Therefore, conventional technologies such as viral culture are being abandoned in favour of methods that provide rapid diagnosis such as antigen detection and molecular (e.g. RT–PCR based) diagnosis. These last methods detect the presence of only a pre-selected agent: they are not 'open ended' methods able to detect the unexpected! It is, however, equally clear that once the candidate agent had been identified, the approaches of modern molecular biology made short shrift of the complete genetic characterization of the virus.

In the context of increasing preoccupation with bio-terrorist threats, SARS reminds us that 'nature' remains the greatest bio-terrorist threat of all. It is desirable that the funds and resources pouring into combating bio-terrorism be targeted generically, in ways that help our capacity to confront the certainty of naturally emerging infectious diseases as well as uncertain possibilities of bio-terrorist attacks. Most recent emerging infectious disease threats have been zoonoses arising from microbes crossing the species barrier to humans (Osterhaus 2001).

SARS vividly illustrated that we indeed live in a global village in relation to emerging infectious disease. SARS also illustrated that emerging infectious diseases are not just threats to human health but can radically impact on the economy and society as a whole. Given the rapid dissemination of SARS through air travel, its control required a coordinated and global response. WHO was able to mobilize and coordinate a rapid global response that was instrumental in understanding and controlling SARS. The speed and extent of success of such intervention is dependent on national governments.

SARS manifested several features that made it more amenable to control through public health measures than some other potential emerging infectious disease threats. Most important of these was the fact that there was little or no transmission of SARS-CoV in the late incubation period or even in the first few days of illness. Furthermore, asymptomatic infection seemed to be less common and less epidemiologically relevant than with many other respiratory viral infections. It is salutary to keep in mind that the next global emerging infectious disease threat may not be so amenable to interruption by case detection and isolation, once human-to-human transmission is established. The current threat from avian influenza subtype H5N1 is a case in point (WHO 2004). The parallels with SARS are poignant. As with SARS in late 2002, there are now repeated inter-species transmission events of H5N1 virus from the avian reservoir to humans and other mammalian species. In this instance, the intensity and geographical scale over which these events are occurring are vastly greater than was the case with SARS. 'Wet markets' where live animals are sold for human consumption play a role in both diseases (Guan *et al.* 2003; Webster 2004). At the time of writing, transmission of influenza H5N1 to humans is inefficient, and has so far not resulted in efficient human-to-human transmission. However, if left unchecked, as occurred with SARS in late 2002, it is possible that the virus may acquire the property of efficient human-to-human transmission, either through reassortment or mutation of the viral genome. Once adapted to human-to-human transmission, influenza is highly transmissible, both in the late incubation period as well as early in the disease. Therefore, its spread may not be amenable to interruption with the same public health measures used to successfully contain SARS. The recent reports that the influenza pandemic of 1918 may have been caused by an avian virus directly adapting to human transmission (rather than reassorting with a pre-existing human virus) provides an ominous portent (Stevens *et al.* 2004).

This article is dedicated to the healthcare professionals in Hong Kong and elsewhere who risked their lives in the service of their profession, some of them making the ultimate sacrifice. Our own colleagues who played a key role in the discovery of the aetiology of SARS, in developing diagnostic tests and unravelling some of its mysteries include K. H. Chan, J. M. Nicholls, L. L. M. Poon, W. L. Lim, V. C. C Cheng, C. M.

Chu, K. S. Chan, I. F. Hung, S. T. Lai, T. K. Ng, W. H. Seto, D. Tsang, L. Yam, W. C. Yam, B. J. Zheng, R. Yung, K. Y. Yuen and many others in the University of Hong Kong, the Hospital Authority of Hong Kong and the Department of Health, Hong Kong SAR.

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GLOSSARY

RT–PCR: reverse transcription–polymerase chain reaction
SAR: Special Administrative Region
SARS: severe acute respiratory syndrome
SARS-CoV: severe acute respiratory syndrome coronavirus
WHO: World Health Organization